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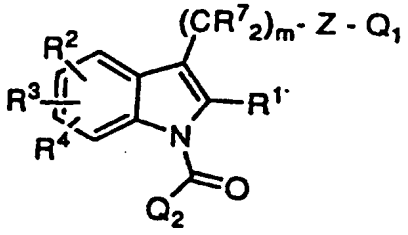
(54) Title: INDOLE DERIVATIVES WITH AFFINITY FOR THE CANNABINOID RECEPTOR

(57) Abstract

Disclosed are indole derivatives of formula (I) having activity on the cannabinoid receptors and the methods of their preparation. The compounds are useful for lowering ocular intraocular pressure and treating glaucoma because of the activity of the cannabinoid receptor.




(I)

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| TT | Trinidad and Tobago |
| UA | Ukraine |
| UG | Uganda |
| US | United States of America |
| UZ | Uzbekistan |
| VN | Viet Nam |

TITLE OF THE INVENTION

# INDOLE DERIVATIVES WITH AFFINITY FOR THE CANNABINOID RECEPTOR

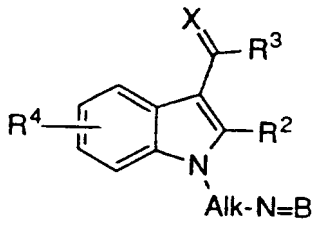
## BACKGROUND OF THE INVENTION

The terms cannabinoid or cannabimimetic compound apply to compounds which produce a physiological effect similar to that of the plant Cannabis Sativa, or a compound that has affinity for the cannabinoid receptors $CB_1$ or $CB_2$. See Matsuda, L.; Lolait, S.J.; Brownstein,M.J.; Young, A.C.; Bonner, T.I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, **1990**, *346*, 561-564: Munro, S.; Thomas, K.L.; Abu-Shaar, M. Molecular characterization of the peripheral receptor of cannabinoids. *Nature*, **1993**, *1993*, 61-65. Examples of such compounds are $\Delta^9$-THC and its analogs (Razdan, R.K. Structure activity relationship in the cannabinoids. *Pharmacol. Rev.*, **1986**, *38*, 75-149), WIN-55212-2 and its analogs (D'Ambra, T.E.; Estep, K.G.; Bell, M.R.; Eissenstat, M.A.; Josef, K.A.; Ward, S.J.; Haycock, D.A.; Baizman, E.R.; Casiano, F.M.; Beglin, N.C.; Chippari, S.M.; Grego, J.D.; Kullnig, R.K.; Daley, G.T. Conformationnaly restrained analogues of Pravadoline: Nanomolar potent, enantioselective, aminoalkylindole agonist of the cannabinoid receptor. *J. Med. Chem.*, **1992**, *35*, 124-135: Bell, M.R.; D'Ambra, T.E.; Kumar, V.; Eissenstat, M.A.; Hermann, J.L.; Wetzel, J.R.; Rosi, D.; Philion, R.E.; Daum, S.J.; Hlasta, D.J.; Kullnig, R.K.; Ackerman, J.H.; Haubrich, D.R.; Luttinger, D.A.; Baizman, E.R.; Miller, M.S.; Ward, S.J. Antinociceptive aminoalkylindoles. *J. Med. Chem.*, **1991**, *34*, 1099-1100), CP-55940 and its analogs (Johnson, M.R.; Melvin, L.S. The discovery of non-classical cannabinoid analgetics. In "Cannabinoids as therapeutic agents", **1986**, Mechoulam, R., Ed., CRC Press: Boca Raton FL, pp.121-145), SR141716A and its analogs (Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Rinaldi, M. Nouveaux derives du pyrazole, procede pour leur preparation et composition pharmaceutiques les contenant. French Patent 2692575-A1, **1992**: Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat,

G.; Caput. D.; Ferrara, P.; Soubrie, P.; Breliere, J-C.; Le Fur, G.; Rinaldi-Carmona, M. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. International Cannabis Research Society Conference Abstract, **July 1994**, L'EstÈrel, Canada, p. 33), and anandamide (Devane, W.A.; Hanus, L.; Breuer, A.; Pertwee, R.G.; Stevenson, L.A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, **1992**, *258*, 1946-1949) and its analogs. Anandamide has been termed the endogenous ligand of the $CB_1$ receptor, as it is synthesized near its site of action and is potent and selective for the $CB_1$ receptor.

The biological activity of cannabinoids has been extensively reviewed. See Hollister, L.E. Health aspects of Cannabis. *Pharmacol. Rev.*, **1986**, *38*, 1-20. Their usefulness in various disease states has been discussed. See The therapeutic potential of marihuana. Cohen, S. and Stillman, R.C., eds. Plenum: New York, **1976**.

Additionally, US patents 4,973,587 and 5,013,837 (Ward et al.) disclose compounds of formula 1:




1

having antiglaucoma compositions where:

$R_2$ is hydrogen, lower alkyl, chloro or fluoro;

$R_3$ is phenyl ( or phenyl substituted by from one to three substituents selected from halogen, lower alkoxy, lower alkoxymethyl, hydroxy, lower alkyl, amino, lower alkylamino, di-lower alkylamino or lower alkylmercapto), methylenedioxyphenyl, benzyl, styryl, lower alkoxystyryl,

1- or 2-naphthyl, ) or 1- or 2-naphthyl substituted by from one to two substituents selected from lower alkyl, lower alkoxy, halo or cyano), (1H-imidazol-1-yl)naphthyl, 2-(1-naphthyl)ethenyl,1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl, pyrenyl,2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2or 3-benzo[b]thienyl, 5-(1H- benzimidazolyl) or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl;

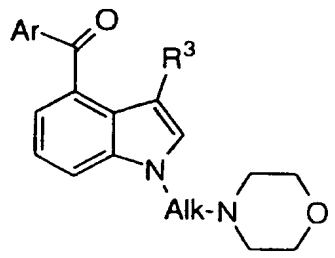
$R_4$ is hydrogen or lower alkyl, hydroxy, lower alkoxy or halo in the 4-, 5-, 6- or 7-positions;

X is O or S;

Alk is lower alkylene having the formula $(CH_2)_n$ where n is the integrer 2 or 3, or such lower-alkylene substituted by a lower-alkyl group; and

N=B is N,N-di-lower alkylamino, 4-morpholinyl, 2-lower alkyl-4-morpholinyl, 3-lower alkylmorpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 3-hydroxy-1-piperidinyl.

US patent 5,081,122 (Ward) discloses compounds of formula 2:

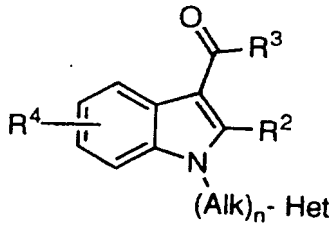



2

having antiglaucoma compositions where:
Ar is lower alkoxyphenyl or 1- or 2-naphthyl;
$R_3$ is hydrogen or lower alkyl;
Alk is lower alkylene containing from two to four carbon atoms.

The present compounds differ from Ward's (formula 1 and 2) primarily in having a carbonyl on the nitrogen of the indole while it is at the 4-position in the case of the US patent 5,081,122.

EP 0 444 451 generically discloses a compound of formula 3:



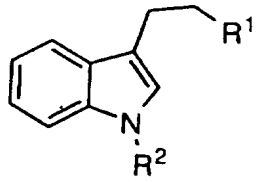

3

useful as analgesic, anti-rheumatic, anti-inflammatory or anti-glaucoma agents where:

| | |
|---|---|
| $R_2$ | is hydrogen, lower alkyl; |
| $R_3$ | is phenyl ( or phenyl substituted by from one to three substituents selected from halogen, lower alkoxy, hydroxy, lower alkyl, nitro, amino, lower alkylamino, di-lower alkylamino, loweralkylmercapto, lower alkylsulfinyl, lower alkylsulfonyl and methylenedioxy), 2- or 4-biphenyl or 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower alkyl, lower alkoxy, halogen, lower alkylmercapto, lower alkylsulfinyl, lower alkylsulfonyl and trifluoromethyl); |
| $R_4$ | is hydrogen or from one to two substituents selected from loweralkyl, hydroxy, lower alkoxy, and halogen at the 4-, 5-, 6- or 7- positions; |
| Alk | is lower alkylene containing from two to four carbon atoms which may contain a lower alkyl group; |
| n | is 0 or 1; |
| Het | is an aliphatic heterocycle, 2-piperazinyl and 2-indolinyl. |

The present compound differs from formula 3 primarily in having a carbonyl on the nitrogen of the indole.

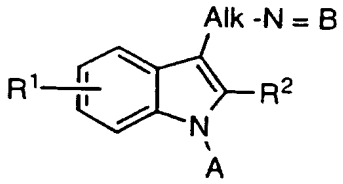
U.S. Patent 3,489,770 generically discloses compound having the following formula 4:




4

The compounds are said to have anti-inflammatory, hypotensive, hypoglycemic and CNS activities. Although not within the ambit of the above-defined genus, the patent also discloses a variety of species where $R_2$ is an arylcarbonyl group.

British Patent 1,374,414 and U.S. Patent 4,021,431 generically discloses compounds having the following structural formula 5:




5

The compounds are useful as anti-inflammatory agents. Although not within the ambit of the above-defined genus, the patent also discloses a variety of species where A is an arylcarbonyl group.

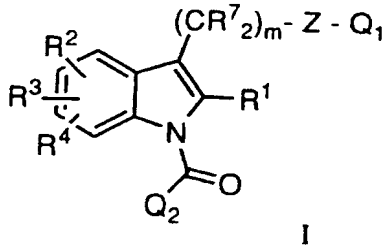
## SUMMARY OF THE INVENTION

The present invention relates to indoles having activity on the cannabinoid receptor CB2 and the methods of their preparation.

Because of this activity on the cannabinoid receptor, the compounds of the present invention are useful for lowering the IOP (intra ocular pressure).

## DETAIL DESCRIPTION OF THE INVENTION

The compounds of the invention can be summarized by formula I:



I

wherein:

$R^1$ is H, lower alkyl, aryl, benzyl, or lower fluorinated alkyl;

$R^{2-4}$ is independently, H, lower alkyl, lower fluorinated alkyl, halogen, $NO_2$, CN, $-(CR^7_2)m-OR^1$, $-(CR^7_2)m-S(O)nR^6_2$, or $-(CR^7_2)m-R^6$;

$R^5$ is H, lower alkyl, aryl, or benzyl;

$R^6$ is lower alkyl, aryl, benzyl, or $N(R^5)_2$;

$R^7$ is H, or lower alkyl;

$R^8$ is $R^7$, lower fluorinated alkyl, halogen, $OR^7$, or lower alkyl thio;

$R^9$ is $R^7$, lower fluorinated alkyl, halogen, $OR^7$, or lower alkyl thio;

$Q_1$ is H, $OR^7$, CHO, CN, $CO_2R^7$, $C(O)SR^7$, $S(O)_nR^6$, HET or $N(R^7)_2$, wherein two $R^7$ groups may be joined to form a

pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine ring and their quaternary methyl ammonium salts;

$Q_2$ is phenyl, naphthyl, quinolinyl, furanyl, thienyl, pyridinyl, anthracyl, benzothienyl, benzofuranyl or thieno[3,2-b]-pyridinyl, mono-, di- or trisubstituted with $R^8$;

HET is is a diradical of benzene, thiazole, thiophene, or furan, substituted with one or two $R^9$ groups;

Z is CO or a bond.

m is 0-6; and

n is 0,1, or 2.

Definitions

The following abbreviations have the indicated meanings:

| | | |
|---|---|---|
| DCC | = | 1,3-dicyclohexylcarbodiimide |
| DIBAL | = | diisobutyl aluminum hydride |
| DMAP | = | 4-(dimethylamino)pyridine |
| DMF | = | N,N-dimethylformamide |
| DMSO | = | dimethyl sulfoxide |
| HMPA | = | hexamethylphosphoramide |
| KHMDS | = | potassium hexamethyldisilazane |
| LDA | = | lithium diisopropylamide |
| MCPBA | = | metachloroperbenzoic acid |
| Ms | = | methanesulfonyl = mesyl |
| MsO | = | methanesulfonate = mesylate |
| NBS | = | N-bromosuccinimide |
| PCC | = | pyridinium chlorochromate |
| PDC | = | pyridinium dichromate |
| Ph | = | phenyl |
| PPTS | = | pyridinium p-toluene sulfonate |
| pTSA | = | p-toluene sulfonic acid |
| Pye | = | pyridinediyl |

| | | |
|---|---|---|
| r.t. | = | room temperature |
| rac. | = | racemic |
| Tf | = | trifluoromethanesulfonyl = triflyl |
| TfO | = | trifluoromethanesulfonate = triflate |
| THF | = | tetrahydrofuran |
| THP | = | tetrahydropyran-2-yl |
| TLC | = | thin layer chromatography |
| Ts | = | p-toluenesulfonyl = tosyl |
| TsO | = | p-toluenesulfonate = tosylate |
| Tz | = | 1H (or 2H)-tetrazol-5-yl |
| $SO_2$ | = | =O=S=O |

Alkyl group abbreviations

| | | |
|---|---|---|
| Me | = | methyl |
| Et | = | ethyl |
| n-Pr | = | normal propyl |
| i-Pr | = | isopropyl |
| n-Bu | = | normal butyl |
| i-Bu | = | isobutyl |
| s-Bu | = | secondary butyl |
| t-Bu | = | tertiary butyl |

The term alkyl means linear, branched, and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, s- and t-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclohexylmethyl, and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

"Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration.

Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -$SCH_2CH_2CH_3$.

"Aryl" includes phenyl and phenyl monosubstituted by halogen, a lower alkoxy or a lower alkylthio group.

"Lower fluorinated alkyl" means alkyl groups of from 1 to 7 carbon atoms in which one or more of the hydrogen atoms has been replaced by fluorine.

"Benzyl" includes mono or disubstitution on the aromatic ring by halogen, lower alkoxy or lower alkylthio groups. The hydrogens of the methylene moiety could be replace by lower alkyl.

Halogen includes F, Cl, Br, and I.

It is intended that the definition of any substituent (e.g., $R^5$) in a particular molecule be independent of its definition elsewhere in the molecule. Thus, -$N(R^5)_2$ represents -NHH, -$NHCH_3$, -$NHC_6H_5$, etc.

Optical Isomers - Diastereomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from

pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Examples of the novel compounds of this invention are as follows:

TABLE 1 *m = 1 EXCEPT NOTED OTHERWISE

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^7$ * | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 2 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 3 | $CH_3$ | H | H | Br | H | - | 4- MORPHOLINE | 2-CHLOROPHENYL |
| 4 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 5 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 6 | $CH_3$ | H | H | $C_2F_5$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 7 | $CH_3$ | H | H | $NO_2$ | H | - | 4- MORPHOLINE | 2-CHLOROPHENYL |
| 8 | $CH_3$ | H | H | Ph | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 9 | $CH_3$ | H | H | $NH_2$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 10 | $CH_3$ | H | H | $N(CH_3)_2$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 11 | $CH_3$ | H | H | $N(Bn)_2$ | H | - | 4- MORPHOLINE | 2-CHLOROPHENYL |
| 12 | $CH_3$ | H | H | $N(Ph)_2$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 13 | $CH_3$ | H | H | CN | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 14 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 15 | $CH_3$ | H | H | $SO_2Ph$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 16 | $CH_3$ | H | H | $SO_2NH_2$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 17 | $CH_3$ | H | H | $SO_2NHCH_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 18 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 19 | $CH_3$ | H | H | $CH_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 20 | $CH_3$ | H | H | $C_2H_5$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 21 | $CH_3$ | H | H | n-$C_3H_7$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 22 | $CH_3$ | H | H | OH | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 23 | $CH_3$ | H | H | $OC_2H_5$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 24 | $CH_3$ | H | H | $OC_3H_7$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 25 | $CH_3$ | H | H | OPh | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 26 | $CH_3$ | H | H | OBn | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 27 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 28 | $CH_3$ | H | H | Cl | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 29 | $CH_3$ | H | H | F | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 30 | $CH_3$ | H | H | Br | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 31 | $CH_3$ | H | H | $OCH_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 32 | $CH_3$ | H | H | $CF_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 33 | $CH_3$ | H | H | $C_2F_5$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 34 | $CH_3$ | H | H | $NO_2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 35 | $CH_3$ | H | H | Ph | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 36 | $CH_3$ | H | H | $NH_2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 37 | $CH_3$ | H | H | $N(CH_3)2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 38 | $CH_3$ | H | H | $N(Bn)_2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 39 | $CH_3$ | H | H | $N(Ph)_2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 40 | $CH_3$ | H | H | CN | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 41 | $CH_3$ | H | H | $SO_2CH_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 42 | $CH_3$ | H | H | $SO_2Ph$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 43 | $CH_3$ | H | H | $SO_2NH_2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 44 | $CH_3$ | H | H | $SO_2NHCH_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 45 | $CH_3$ | H | H | $SO_2NCH_3)2$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 46 | $CH_3$ | H | H | $CH_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 47 | $CH_3$ | H | H | $C_2H_5$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 48 | $CH_3$ | H | H | n-$C_3H_7$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 49 | $CH_3$ | H | H | OH | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 50 | $CH_3$ | H | H | $OC_2H_5$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 51 | $CH_3$ | H | H | $OC_3H_7$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 52 | $CH_3$ | H | H | OPh | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 53 | $CH_3$ | H | H | OBn | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 54 | $CH_3$ | H | H | $OCF_3$ | H | CO | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 55 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 56 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 57 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 58 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 59 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 60 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 61 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 62 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 63 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 64 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 65 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 66 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 67 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 68 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 69 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 70 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 71 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 72 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 73 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 74 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 75 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 76 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 77 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 2-NAPHTHYL |
| 78 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 2-NAPHTHYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 79 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 2-THIENYL |
| 80 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 2-THIENYL |
| 81 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 2-THIENYL |
| 82 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 2-THIENYL |
| 83 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 2-THIENYL |
| 84 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 2-THIENYL |
| 85 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 2-THIENYL |
| 86 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 2-THIENYL |
| 87 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 88 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 89 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 90 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 91 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 92 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 93 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 94 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-THIENYL |
| 95 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 96 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 97 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 98 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 99 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 100 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 101 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 102 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 3,4,5-TRICHLORO-2-THIENYL |
| 103 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 2-FURANYL |
| 104 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 2-FURANYL |
| 105 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 2-FURANYL |
| 106 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 2-FURANYL |
| 107 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 2-FURANYL |
| 108 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 2-FURANYL |
| 109 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 2-FURANYL |
| 110 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 2-FURANYL |
| 111 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 112 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 113 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 114 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 115 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 116 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 117 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |
| 118 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 5-CHLORO-2-FURANYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 119 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 3-FURANYL |
| 120 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 3-FURANYL |
| 121 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 3-FURANYL |
| 122 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 3-FURANYL |
| 123 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 3-FURANYL |
| 124 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 3-FURANYL |
| 125 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 3-FURANYL |
| 126 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 3-FURANYL |
| 127 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 3-THIENYL |
| 128 | $CH_3$ | H | H | F | H | - | 4-MORPHOLINE | 3-THIENYL |
| 129 | $CH_3$ | H | H | Cl | H | - | 4-MORPHOLINE | 3-THIENYL |
| 130 | $CH_3$ | H | H | $OCH_3$ | H | - | 4-MORPHOLINE | 3-THIENYL |
| 131 | $CH_3$ | H | H | $OCF_3$ | H | - | 4-MORPHOLINE | 3-THIENYL |
| 132 | $CH_3$ | H | H | $CF_3$ | H | - | 4-MORPHOLINE | 3-THIENYL |
| 133 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 4-MORPHOLINE | 3-THIENYL |
| 134 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 4-MORPHOLINE | 3-THIENYL |
| 135 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 136 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 137 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 138 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 139 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 140 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 141 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 142 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 143 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 144 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 145 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 146 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 147 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 148 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 149 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 150 | $CH_3$ | H | H | $SO_2N(CH_3)2$ | H | - | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 151 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 152 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 153 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 154 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 155 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 156 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 157 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 158 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 1-NAPHTHYL |
| 159 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 160 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 161 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 162 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 163 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 164 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 165 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 166 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 2-NAPHTHYL |
| 167 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 168 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 169 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 170 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 171 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 172 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 173 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 174 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 2-THIENYL |
| 175 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 176 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 177 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 178 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 179 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 180 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 181 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 182 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-THIENYL |
| 183 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 184 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 185 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 186 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 187 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 188 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 189 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 190 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 3,4,5-TRICHLORO-2-THIENYL |
| 191 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 192 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 193 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 194 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 195 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 196 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 197 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 2-FURANYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 198 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 2-FURANYL |
| 199 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 200 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 201 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 202 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 203 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 204 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 205 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 206 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 3-FURANYL |
| 207 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 208 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 209 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 210 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 211 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 212 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 213 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 214 | $CH_3$ | H | H | $SO_2N(CH_3)_2$ | H | - | 1-PIPERIDINYL | 5-CHLORO-2-FURANYL |
| 215 | $CH_3$ | H | H | H | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 216 | $CH_3$ | H | H | F | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 217 | $CH_3$ | H | H | Cl | H | - | 1-PIPERIDINYL | 3-THIENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 218 | $CH_3$ | H | H | $OCH_3$ | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 219 | $CH_3$ | H | H | $OCF_3$ | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 220 | $CH_3$ | H | H | $CF_3$ | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 221 | $CH_3$ | H | H | $SO_2CH_3$ | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 222 | H | H | H | $SO_2N(CH_3)2$ | H | - | 1-PIPERIDINYL | 3-THIENYL |
| 223 | H | H | H | Cl | H | - | $(CH_3)_3N^+$ | 2-CHLOROPHENYL |
| 224 | H | H | H | $OCH_3$ | H | - | $(CH_3)_3N^+$ | 2,3-DICHLOROPHENYL |
| 225 | H | H | H | Cl | H | - | 2-PYRIDINYL | 2-CHLOROPHENYL |
| 226 | H | H | H | $OCH_3$ | H | - | 2-PYRIDINYL | 2,3-DICHLOROPHENYL |
| 227 | H | H | H | Cl | H | - | 1-PYRROLIDINYL | 9-ANTHRACYL |
| 228 | H | H | H | $OCH_3$ | H | - | 1PYRROLIDINYL | 9-ANTHRACYL |
| 229 | H | H | H | Cl | H | - | 2-PYRIDINYL | 2-CHLOROPHENYL |
| 230 | H | H | H | $OCH_3$ | H | - | 2-PYRIDINYL | 2,3-DICHLOROPHENYL |
| 231 | H | H | H | Cl | H | - | 2-PYRROLIDINYL | 9-ANTHRACYL |
| 232 | H | H | H | $OCH_3$ | H | - | 2-PYRROLIDINYL | 9-ANTHRACYL |
| 233 | H | H | H | Cl | H | - | 1-PIPERAZINYL | 2-CHLOROPHENYL |
| 234 | H | H | H | $OCH_3$ | H | - | 2-PIPERAZINYL | 2,3-DICHLOROPHENYL |
| 235 | H | H | H | Cl | H | - | PHENYL | 9-ANTHRACYL |
| 236 | $CH_3$ | H | H | $OCH_3$ | H | - | PHENYL | 2-CHLOROPHENYL |
| 237 | $CH_3$ | H | H | Cl | H | - | PHENYL | 2,3-DICHLOROPHENYL |

TABLE 1 (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 238 | $CH_3$ | H | H | $OCH_3$ | H | - | 2-CHLOROPHENYL | 9-ANTHRACYL |
| 239 | $CH_3$ | H | H | Cl | H | - | 2,3-DICHLOROPHENYL | 2-CHLOROPHENYL |
| 240 | $CH_3$ | H | H | $OCH_3$ | H | - | 2-THIENYL | 2,3-DICHLOROPHENYL |
| 241 | $CH_3$ | H | H | Cl | H | - | 3-THIENYL | 2-CHLOROPHENYL |
| 242 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PIPERIDINYL | 2-CHLOROPHENYL |
| 243 | $CH_3$ | H | H | Cl | H | CO | 1-PIPERIDINYL | 2,3-DICHLOROPHENYL |
| 244 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PIPERIDINYL | 9-ANTHRACYL |
| 245 | $CH_3$ | H | H | Cl | H | CO | 1-PIPERIDINYL | 2-THIENYL |
| 246 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PIPERIDINYL | 3-THIENYL |
| 247 | $CH_3$ | H | H | Cl | H | CO | 1-PIPERIDINYL | 2-FURANYL |
| 248 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PIPERIDINYL | 3-FURANYL |
| 249 | $CH_3$ | H | H | Cl | H | CO | 1-PIPERIDINYL | 1-NAPHTHYL |
| 250 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PIPERIDINYL | 2-NAPHTHYL |
| 251 | $CH_3$ | H | H | Cl | H | CO | 1-PYRROLIDINYL | 2-CHLOROPHENYL |
| 252 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PYRROLIDINYL | 2,3-DICHLOROPHENYL |
| 253 | $CH_3$ | H | H | Cl | H | CO | 1-PYRROLIDINYL | 9-ANTHRACYL |
| 254 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PYRROLIDINYL | 2-THIENYL |
| 255 | $CH_3$ | H | H | Cl | H | CO | 1-PYRROLIDINYL | 3-THIENYL |
| 256 | $CH_3$ | H | H | $OCH_3$ | H | CO | 1-PYRROLIDINYL | 2-FURANYL |
| 257 | $CH_3$ | H | H | H | H | CO | 4-MORPHOLINE | 1-NAPHTHYL |

TABLE I (CONTINUED)

| CPD | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^{7*}$ | Z | $Q_1$ | $Q_2$ |
|---|---|---|---|---|---|---|---|---|
| 258 | $CH_3$ | H | H | $OCH_3$ | H | CO | 4-MORPHOLINE | 2,5-DICHLOROPHENYL |
| 259 | $CH_3$ | H | H | $OCH_3$ | H | CO | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 260 | $CH_3$ | H | H | $OCH_3$ | H | CO | 4-MORPHOLINE | 2-CHLORO-4FLUOROPHENYL |
| 261 | $CH_3$ | H | H | $OCH_3$ | H | CO | 4-MORPHOLINE | 3-CHLOROPHENYL |
| 262 | $CH_3$ | H | H | H | H | - | $COOCH_3$ | 1-NAPHTHYL |
| 263 | $CH_3$ | H | H | H | H(m=2) | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 264 | $CH_3$ | H | H | $OCH_3$ | H(m=2) | - | 4-MORPHOLINE | 2,3-DICHLOROPHENYL |
| 265 | $CH_3$ | H | H | H | H | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 266 | $CH_3$ | H | H | $OCH_3$ | H(m=2) | - | 4-MORPHOLINE | 1-NAPHTHYL |
| 267 | $CH_3$ | H | H | $OCH_3$ | H(m=2) | - | 4-MORPHOLINE | 2-CHLOROPHENYL |
| 268 | $CH_3$ | H | H | H | H(m=2) | - | 4-MORPHOLINE | 2-CHLOROPHENYL |

Elemental analysis was conducted on several of the compounds listed above and the results are shown below.

TABLE 2

| ELEMENTAL ANALYSIS | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | CALCULATED | | | FOUND | | |
| CPD | FORMULA | C | H | N | C | H | N |
| 31 | $C_{23}H_{23}ClN_2O_4$ | 64.71 | 5.43 | 6.56 | 64.78 | 5.69 | 6.42 |
| 63 | $C_{25}H_{23}ClN_2O_2$ | 71.33 | 5.99 | 6.65 | 71.23 | 6.99 | 6.57 |
| 258 | $C_{23}H_{22}Cl_2N_2O_4$ | 59.88 | 4.81 | 6.07 | 59.56 | 4.86 | 6.09 |
| 259 | $C_{23}H_{22}Cl_2N_2O_4$ | 59.88 | 4.81 | 6.07 | 59.25 | 4.89 | 5.81 |
| 260 | $C_{23}H_{22}ClFN_2O_4$ | 62.09 | 4.98 | 6.30 | 62.05 | 5.04 | 6.53 |
| 261 | $C_{23}H_{23}ClN_2O_4$ | 64.71 | 5.43 | 6.56 | 63.36 | 5.29 | 6.47 |
| 263 | $C_{26}H_{27}ClN_2O_2$ | 71.80 | 6.26 | 6.44 | 71.64 | 6.36 | 6.15 |
| | | | | | | | |

The preferred compounds are realized when:

| | |
|---|---|
| $R^1$ is | H, lower alkyl, or lower fluorinated alkyl; |
| $R^{2-4}$ is | independently H, lower alkyl, $OR^1$, halogen, or lower fluorinated alkyl; |
| $R^7$ is | H, or lower alkyl; and |
| $Q_1$ is | morpholine, piperazine, piperidine, or pyrrolidine. |

The most preferred compounds are realized when:

| | |
|---|---|
| $R^1$ is | lower alkyl; |
| $R^{2-4}$ is | independently is H, or $OR^1$; |
| $R^7$ is | H; |
| $Q_1$ is | morpholine; |
| m is | 2; and |
| Z is | a bond. |

Specific compounds are:

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone;

2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole;

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)- 1*H*-indole;

1-(1-Naphthoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(1-Naphthoyl)-5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole; and

1-(2-Chlorobenzoyl)-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole.

Utilities

The ability of the compounds of formula I to mimic the actions of the cannabinoids makes them useful for preventing or reversing the symptoms that can be treated with cannabis, some of its derivatives and synthetic cannabinoids in a human subject. Thus, compounds of formula I are useful to treat, prevent, or ameliorate in mammals and especially in humans:

1- various ocular disorders such as glaucoma.
2- pulmonary disorders including diseases such as asthma, chronic bronchitis and related airway diseases.
3- allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis and the like.
4- inflammation such as arthritis or inflammatory bowel disease.
5- pain.
6- disorders of the immune system such as lupus, AIDS, etc.
7- allograft rejection.
8- central nervous system diseases such as Tourette's syndrome, Parkinson's disease, Huntingdon's disease, epilepsy, various psychotic afflictions such as depression, manic depression, etc.
9- vomiting, and nausea and vertigo, especially in the case of chemotherapy patients.

Dose Ranges

The magnitude of therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration and vary upon the clinician's judgment. It will also vary according to the age, weight and response of the individual patient. An effective dosage amount of the active component can thus be determined by the clinician after a consideration of all the criteria and using is best judgment on the patient's behalf.

An ophthalmic preparation for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, parenteral and ocular (ophthalmic). They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a

pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by

molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

Combinations with Other Drugs

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients or prodrugs thereof. These other active species may be beta-blockers such as timolol, topical carbonic anhydrase inhibitors such as Dorzolamide, systemic carbonic anhydrase inhibitors such as acetolamide, cholinergic agents such as pilocarpine and its derivatives, prostaglandin F receptor agonists such as Latanoprost, ajmaline and its derivatives, b2 adrenergic agonists such as epinephrine, glutamate antagonists, aminosteroids, diuretics, and any other compound used alone or in combination in the treatment of glaucoma. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with a b-blockers, a carbonic anhydrase inhibitor, a pilocarpine derivative or a prostaglandin agonist, the weight ratio of the compound of the Formula I to the other drug will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

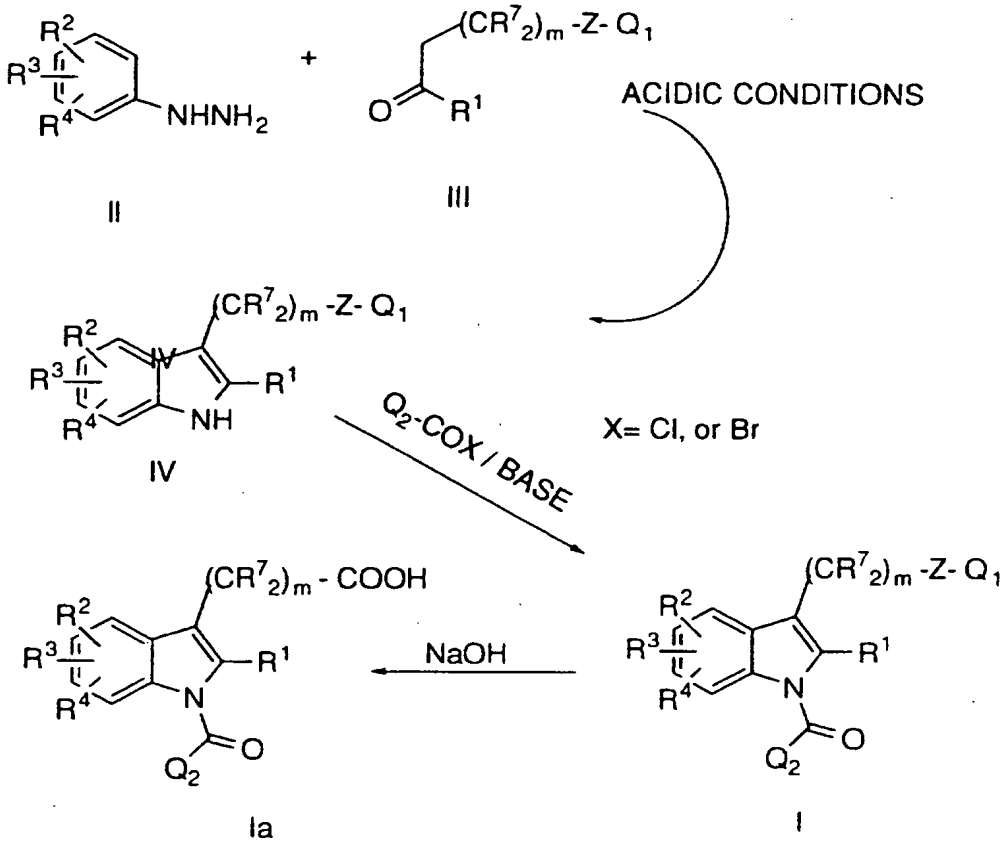
Methods of Synthesis

Compounds of the present invention can be prepared according to the following non-limiting methods. Temperatures are in degrees Celsius.

Method A

The starting indoles used are either commercially available or prepared from an appropiate hydrazine II and a properly substituted aldehyde or ketone III as described in U.S. patent 3,161,654 (incorporated herein). The indole IV obtained is then treated with an acyl chloride or bromide of a properly substituted Q2 and a base to afford the desired indole I. When $Z\text{-}Q^1$ is an ester, it can be hydrolysed to the desired acid Ia with a base such as 1N NaOH in a protic solvent such as MeOH-$H_2O$.

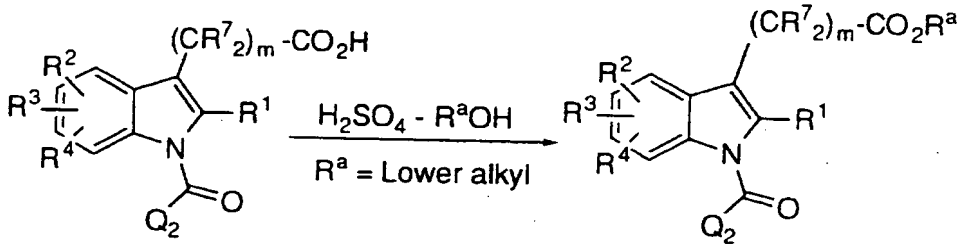
METHOD A



Method B

The acids Ia can be converted to a variety of esters Ib by dissolution in the appropriate lower alkyl alcohol with a strong acid such as 10% $H_2SO_4$ and heated between 60-90° C for 3-12h (Fischer conditions).

METHOD B

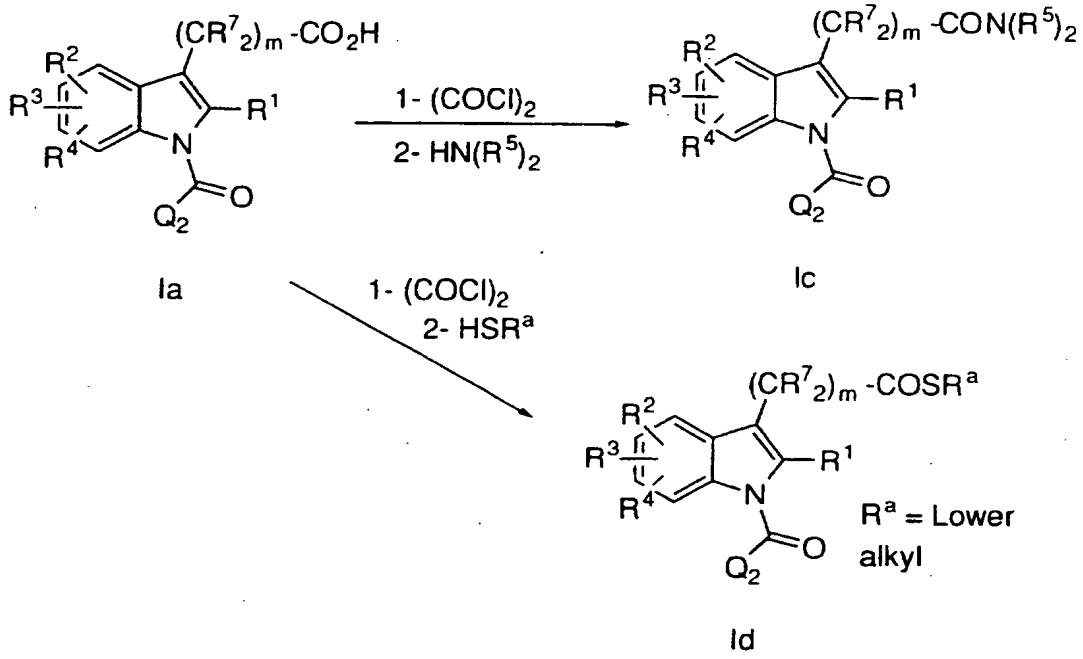



Ia Ib

Method C

Acids Ia are treated with a chlorinating agent such as oxalyl chloride in an inert solvent (methylene chloride, dichloroethane, etc.). The resulting acyl halide is then treated with amines or thiols in the presence of a base (excess amine, Et3N, etc.) to afford the corresponding amide Ic or thiol ester Id.

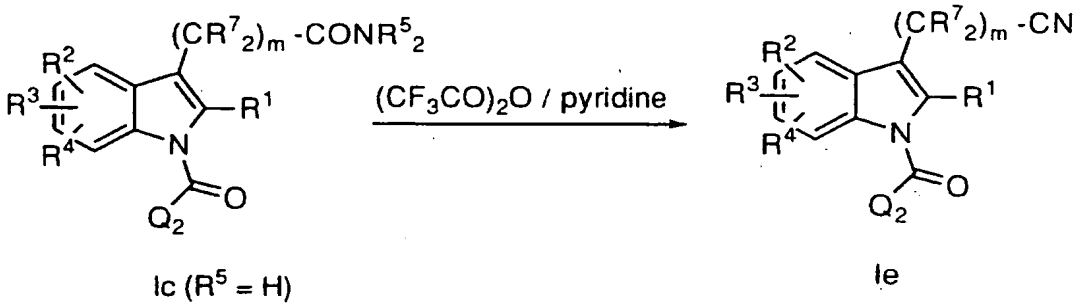
METHOD C




Method D

The primary amides of Ic in an inert solvent such as THF, $Et_2O$, etc. and a base such as pyridine are treated with a dehydrating agent such as trifluoroacetic anhydride at 0° C to afford the nitrile Ie.

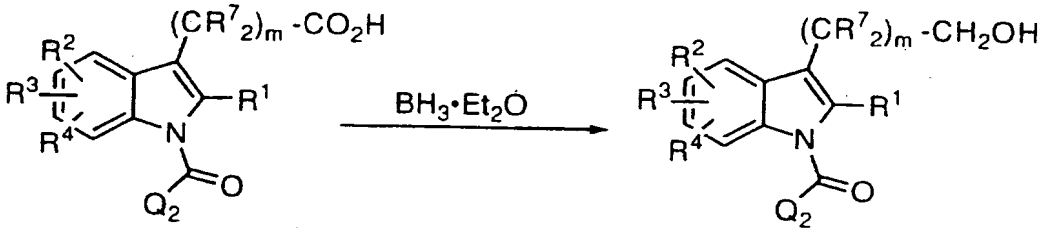
METHOD D



Method E

Acids Ia are treated with borane according to the literature (J.Org. Chem. 1973, **38**, 2786) to afford the alcohols If.

METHOD E

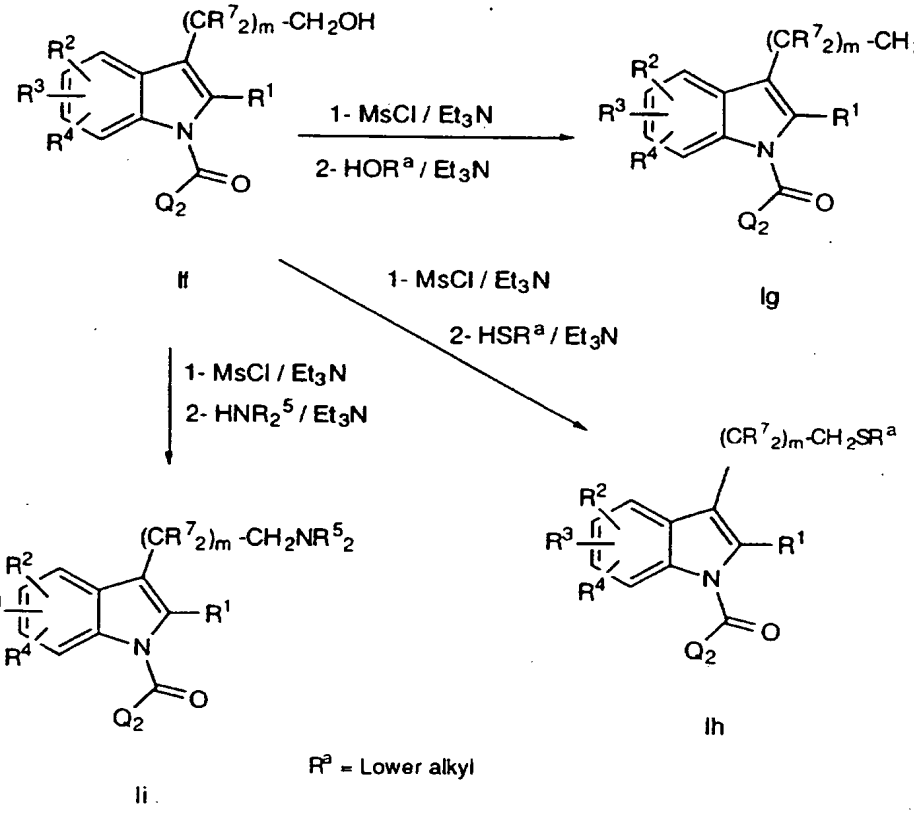



Ia If

Method F

Compounds of type If can be converted to their mesylate or tosylate in an inert solvent such as $CH_2Cl_2$ in the presence of a base such as $Et_3N$ and then reacted with various nucleophiles such as alcohols, thiols and amines to produce compounds Ig, Ih and Ii.

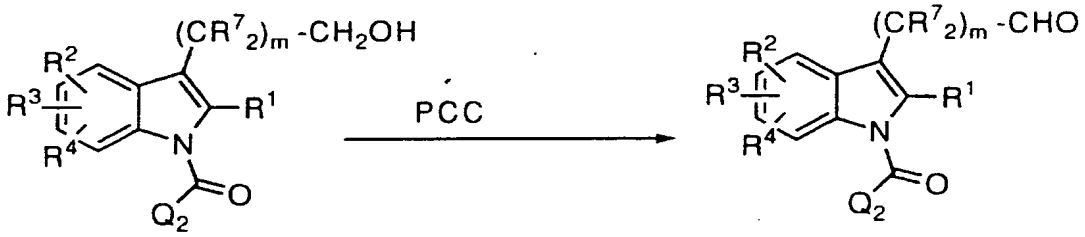
METHOD F



Method G

When compounds of type If are subjected to Swern oxidation (J. Org. Chem. 1978, **43**, 2480), with PCC (Tetrahedron Lett. 1975, 2647) or other oxidizing agents, aldehyde Ij is obtained.

METHOD G

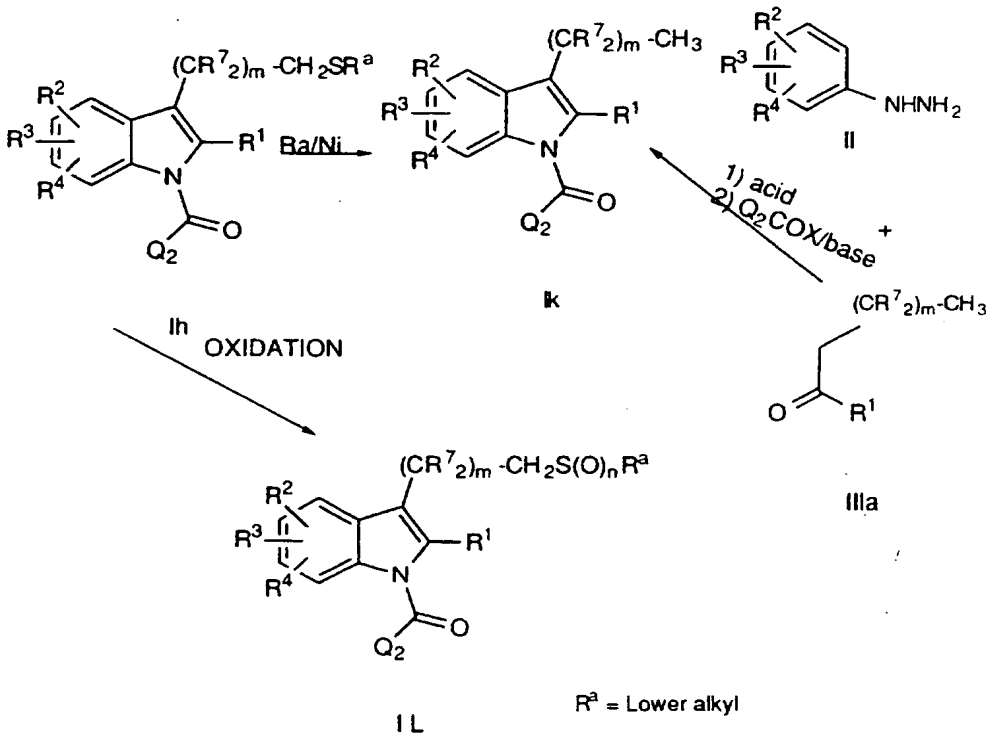



If Ij

Method H

Compounds of type Ih can be reduced to the alkyl chain by reaction with Raney-Nickel in a protic solvent such as ethanol to afford Ik, which can also be prepared by a Fischer indole synthesis starting with an appropriate hydrazine II and a ketone or aldehyde IIIa under acidic conditions. Compound Ih can be oxidized to the sulfoxide or sulfone using for example $H_2O_2$ or MCPBA to give Il.

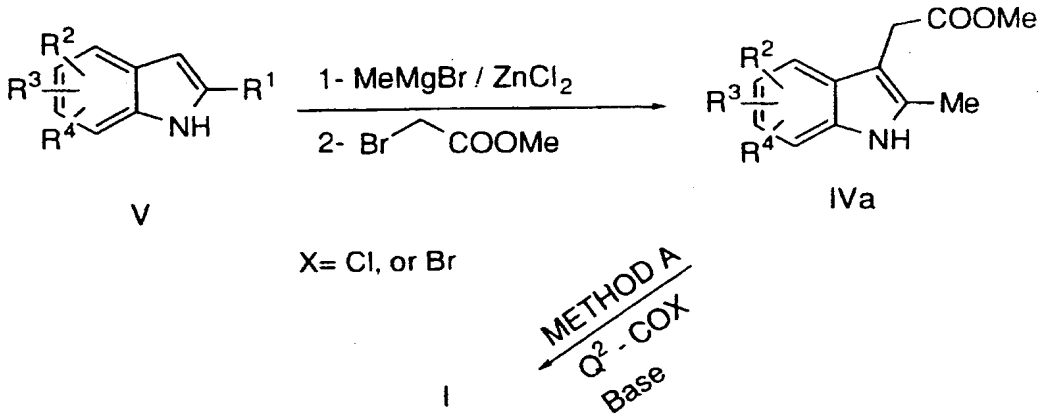
METHOD H



Method I

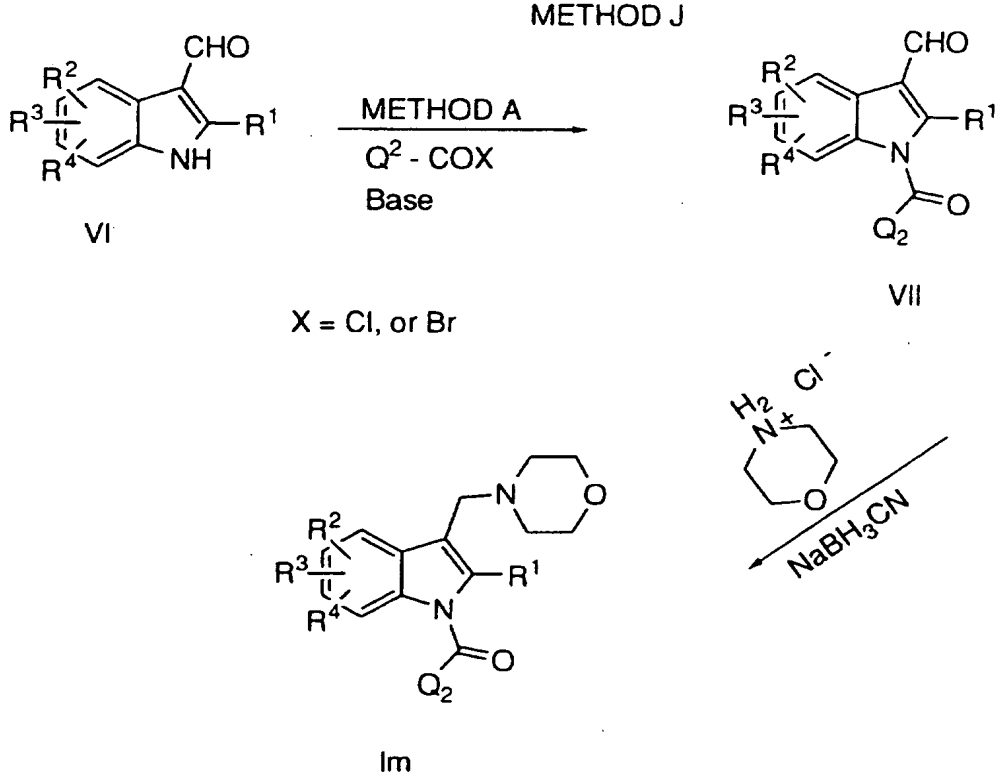
An indole of type V can be deprotonated with a strong base such as MeMgBr, treated with $ZnCl_2$ to exchange the metal when necessary, and an alkylating agent or (other electrophile) added to the mixture to yield compound of type IVa. This in turn according to method A can be converted to a compound of type I.

METHOD I



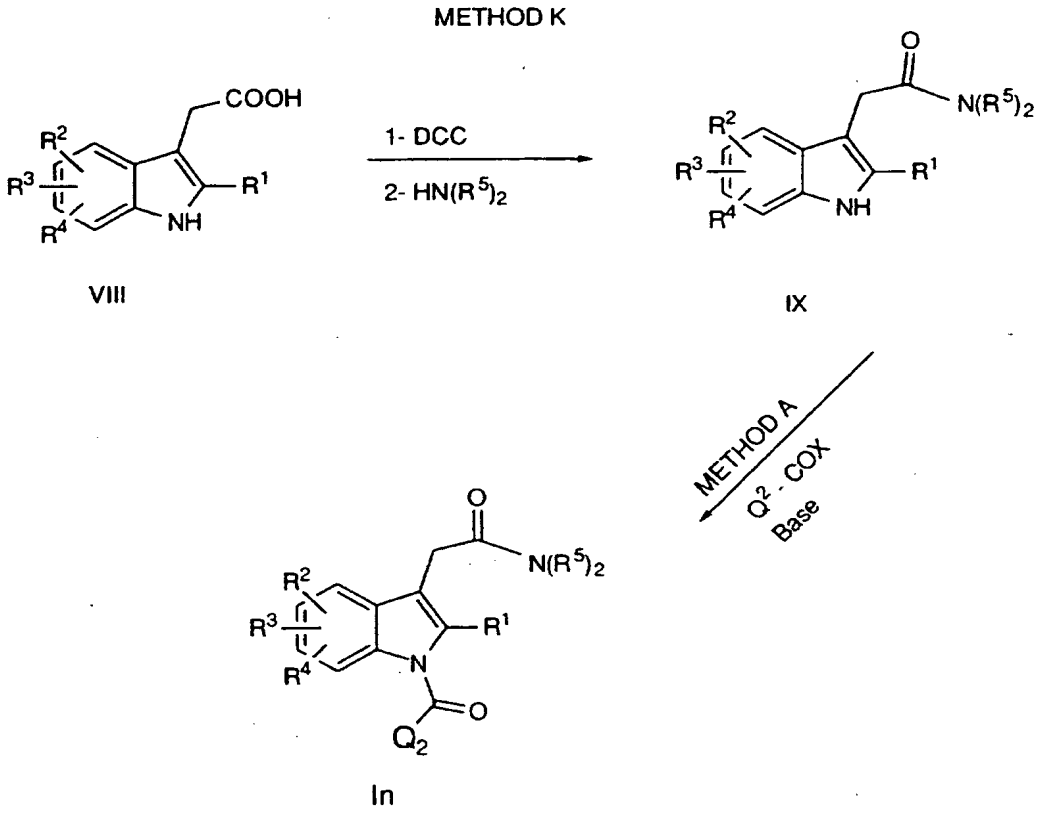
Method J

An indole of type VI can be treated according to method A to yield VII which can be converted to Im with an amine in presence of a reducing agent such as $NaBH_3CN$.



Method K

A carboxylic acidic of type VIII can be coupled with various amines in an inert solvent such as $CH_2Cl_2$ using DCC or the like to yield IX, which can then be converted to In according to method A.




The invention will now be illustrated by the following non-limiting examples (Note: The examples in Table 1, above, that are not illustrated can be made by substantially similar procedures as discussed below) in which, unless stated otherwise:

(i) all operations are carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent is carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions is followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products are assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry, or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data are in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent: conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings: the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL

# INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/CA 96/00080

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0105996 | 25-04-84 | NONE | | |
| US-A-3501465 | 17-03-70 | CH-A- | 485718 | 15-02-70 |
| | | DE-A- | 1595940 | 12-02-70 |
| | | FR-M- | 5205 | 03-07-67 |
| | | FR-A- | 1472042 | 24-05-67 |
| | | GB-A- | 1109884 | |
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INTERNATIONAL SEARCH REPORT

In[illegible]tional application No.
PCT/CA96/00080

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The search for claims 1 and 2 resulted in a large number of novelty destroying compounds. The search for these claims was not complete for economical reasons. (Claims 1 and 2 have been searched incompletely)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/CA 96/00080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP,A,0 444 451 (STERLING DRUG INC) 4 September 1991<br>cited in the application<br>see claims | 1-4 |
| X | JOURNAL OF MEDICINAL CHEMISTRY, vol. 16, no. 2, 1973 WASHINGTON US, pages 176-177,<br>E.W. GLAMKOWSKI 'The aldehyde analog of indomethacin'<br>see the whole document | 1 |
| X | US,A,3 336 194 (TSUNG-YIN SHEN ET AL.) 15 August 1967<br>see claims; examples | 1-3 |
| P,X | GB,A,2 283 745 (MERCK FROSST CANADA INC) 17 May 1995<br>see claims; examples | 1-4 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=156339<br>& CHEM. BER., vol. 46, 1913<br>page 657<br>WEISSGERBER | 1 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=448371<br>& ES,A,341 692 (GALLARDO S.A.) 1967 | 1,2 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=447300<br>& NL,A,6 404 781 (MERCK) 1964 | 1 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=451740<br>& US,A,3 161 654 (MERCK) 1963 | 1 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=493436<br>& BE,A,615 395 (MERCK) 1962 | 1 |
| X | DATABASE CROSSFIRE<br>Beilstein<br>BRN=477362<br>& JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1973 LETCHWORTH GB, pages 13-14, | 1 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/CA 96/00080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/14 A61K31/40 A61K31/405 C07D209/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP,A,0 105 996 (MERCK & CO INC) 25 April 1984<br>see claim 1: Metindol = 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-Indole-3-acetic acid<br>--- | 1-4 |
| X | US,A,3 501 465 (SHEN TSUNG-YING ET AL) 17 March 1970<br>see claims; examples<br>--- | 1 |
| X | US,A,3 489 770 (HERBST DAVID R) 13 January 1970<br>cited in the application<br>see claims; examples<br>---<br>-/-- | 1-3 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 April 1996 | 17.04.96 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | De Jong, B |

Form PCT/ISA/210 (second sheet) (July 1992)

13. Use of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof in the manufacture of a cannabimimetic pharmacological agent selective for CB2 receptors.

bowel disease; pain; disorders of the immune system such as lupus, or AIDS; allograft rejection; central nervous system diseases such as Tourette's syndrome, or Parkinson's disease, or Huntingdon's disease, or epilepsy, or depression, or manic depression; vomiting; or nausea and vertigo; in mammals, including humans, in need thereof, which comprises administering to such a mammal a pharmacologically effective amount of a compound of Claim 1.

8. A composition useful for treating ocular hypertension and glaucoma in a mammal, including humans, in need thereof, which comprises a pharmacologically effective amount of a cannabimimetic pharmacological agent, known to be selective for CB2 receptors, in a carrier or diluent buffered to a pH suitable for ocular administration.

9. A composition useful for treating ocular hypertension and glaucoma in a mammal, including humans, in need thereof, which comprises a pharmacologically effective amount of a cannabimimetic pharmacological agent of Claim 1, known to be selective for CB2 receptors, in a carrier or diluent buffered to a pH suitable for ocular administration.

10. An ocular hypertension and glaucoma pharmaceutical composition comprising a pharmacologically effective amount of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof, in association with a pharmaceutically acceptable carrier.

11. A compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof, for use in treating ocular hypertension and glaucoma; pulmonary disorders; allergies and allergic reactions; or inflammation; pain; disorders of the immune system; allograft rejection; central nervous system diseases; vomiting; or nausea and vertigo.

12. Use of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof as a cannabimimetic pharmacological agent selected for CB2 receptors.

1-(2,3-Dichlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)- 1*H*-indole;

1-(1-Naphthoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(1-Naphthoyl)-5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole; or

1-(2-Chlorobenzoyl)-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole.

5. A method of treating ocular hypertension and glaucoma, which comprises the step of ocularly administering a pharmacologically effective amount of a cannabimimetic pharmacological agent known to be selective for CB2 receptors to a patient in need of such treatment.

6. A method of treating ocular hypertension and glaucoma, which comprises the step of ocularly administering a pharmacologically effective amount of a compound of Claim 1, to a patient in need of such treatment.

7. A method of alleviating, treating or preventing, pulmonary disorders such as asthma, or chronic bronchitis; allergies and allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis; inflamation such as arthritis or inflammatory

$Q_2$ is phenyl, naphthyl, quinolinyl, furanyl, thienyl, pyridinyl, anthracyl, benzothienyl, benzofuranyl or thieno[3,2-b]-pyridinyl, mono-, di- or trisubstituted with $R^8$;

HET is is a diradical of benzene, thiazole, thiophene, or furan, substituted with one or two $R^9$ groups;

Z is CO or a bond.

m is 0-6; and

n is 0,1, or 2.

2. The compounds of Claim 1, wherein,

$R^1$ is H, lower alkyl, or lower fluorinated alkyl;

$R^{2-4}$ is independently H, lower alkyl, $OR^1$, halogen, or lower fluorinated alkyl;

$R^7$ is H, or lower alkyl; and

$Q_1$ is morpholine, piperazine, piperidine, or pyrrolidine.

3. The compounds of Claim 1, wherein

$R^1$ is lower alkyl;

$R^{2-4}$ is independently is H, or $OR^1$;

$R^7$ is H;

$Q_1$ is morpholine;

m is 2; and

Z is a bond.

4. The compounds of Claim 1 which are:

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone;

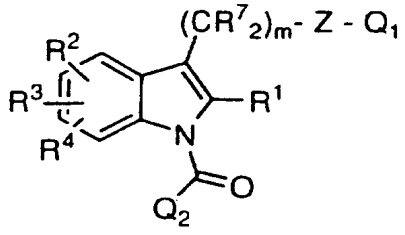
2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole;

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

WHAT IS CLAIMED IS:

1. A compound of the structural formula I:



I

pharmaceutically acceptable salts thereof, or diastereomers,or enantiomers or mixtures thereof,

wherein:

| | |
|---|---|
| $R^1$ is | H, lower alkyl, aryl, benzyl, or lower fluorinated alkyl; |
| $R^{2-4}$ is | independently, H, lower alkyl, lower fluorinated alkyl, halogen, $NO_2$, CN, $-(CR^7_2)m-OR^1$, $-(CR^7_2)m-S(O)nR^6$, or $-(CR^7_2)m-R^6$; |
| $R^5$ is | H, lower alkyl, aryl, or benzyl; |
| $R^6$ is | lower alkyl, aryl, benzyl, or $N(R^5)_2$; |
| $R^7$ is | H, or lower alkyl; |
| $R^8$ is | $R^7$, lower fluorinated alkyl, halogen, $OR^7$, or lower alkyl thio; |
| $R^9$ is | $R^7$, lower fluorinated alkyl, halogen, $OR^7$, or lower alkyl thio; |
| $Q_1$ is | H, $OR^7$, CHO, CN, $CO_2R^7$, $C(O)SR^7$, $S(O)_nR^6$, HET or $N(R^7)_2$, wherein two $R^7$ groups may be joined to form a pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine ring and their quaternary methyl ammonium salts; |

stirred 1h. The mixture was poored in saturated $NaHCO_3$ (25mL), extracted with EtOAc (2x50mL). The organic phase was washed with brine (50mL), dried over $Na_2SO_4$, filtered, concentrated and flash chromatographed (Silica gel ; EtOAc) to yield 503mg (99%) of the title compound.

$^1$NMR ($CDCl_3$, 400MHz) δ 2.12 (s, 3H), 2.52 (m, 6H), 2.79 (t, 2H), 3.74 (t, 4H), 3.82 (s, 3H), 6.71 (dd, 1H), 6.91 (d, 1H), 7.34 (m, 3H), 7.61 (dd, 1H).

Elemental analysis for $C_{23}H_{24}Cl_2N_2O_3$•HCl, calcd: C: 57.1, H: 5.21, N: 5.79; found: C: 57.18, H: 5.26, N: 5.70.

## EXAMPLE 4

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

Step 1: 5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

To 5-methoxy-2-methyl-1H-indole (5.00g ; 31.0mmol) in 30 mL of dry THF at O°C was added dropwise MeMgBr (3.0M in $Et_2O$ ; 11.4mL ; 34.2mmol). The solution was stirred 30 min at r.t. after which $ZnCl_2$ (0.5M in THF ; 64mL ; 32mmol) was added. The mixture was stirred at r.t., after 1h, N-(2-iodoethyl)morpholine (14.41g ; 51.5mmol) was added. The final mixture was stirred at r.t. overnight. The mixture was poored in saturated $NaHCO_3$ (100mL), extracted with EtOAc (2x100mL). The organic phase was washed with brine (100mL), dried over $Na_2SO_4$, filtered, concentrated and flash chromatographed (Silica gel ; EtOAc / Ace O to 10%) to yield 587mg (7%) of the title compound.

$^1$NMR ($CDCl_3$, 400MHz) δ 2.36 (s, 3H), 2.64 (bs, 6H), 2.92 (bs, 2H), 3.83 (bd, 4H), 3.85 (s, 3H), 6.76 (dd, 1H), 6.97 (d, 1H), 7.15 (d, 2H), 7.68 (bs, NH).

Step 2: 1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

To 5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole (311mg ; 1.13mmol) in 10 mL dry THF at -78°C was added HMPA (590µL ; 3.39mmol), then dropwise KHMDS (0.5M in Tol ; 2.5mL ; 1.25mmol). The solution was stirred 30 min at -22°C then cooled to -78°C after which 2,3-dichlorobenzoyl chloride (361mg ; 1.72mmol) was added. The final mixture was allowed to reach r.t. slowly then

$^1$H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 3.64 (s, 3H), 3.68 (s, 2H), 7.05-7.13 (m, 2H), 7.22-7.26 (m, 1H), 7.49-7.52 (m, 1H) and 7.82 (s, 1H).

Step 2: 2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester

The compound of step 1 (1.13g; 5.56 mmol) in 6 mL of DMF was treated with NaH 80% (0.18g; 5.99 mmol) at 25° C. After 30 min a solution of 1-naphthoyl chloride in 5 mL of DMF was added dropwise The reaction mixture was left stirring for 16h and poured into cold water-EtOAc. The organic phase was washed with $H_2O$ (2 X 15 mL) and brine, dried over $Na_2SO_4$ and the solvent removed. Chromatography on silica gel (eluted with 2% EtOAc in toluene) yielded 0.86g (43%) of the title compound.

$^1$H NMR ($CDCL_3$, 400 MHZ) Δ 2.20 (S, 3H), 3.67 (S, 3H), 7.0 (M, 1H), 7.10-7.26 (M, 3H), 7.45-7.60 (M, 5H), 7.95 (M, 1H) AND 8.07 (M, 3H).

High Resolution Mass Spectra results were: Formula ($C_{23}H_{19}NO_3+H^+$); Calculated (358.14415); Found (358.14432)

Step 2: 2-Methyl-3-(morpholin-4-yl)methyl-1-(1naphthoyl)-1H-indole

To the aldehyde (0.118g ; 0.38 mmol) from step 1 and morpholine hydrochloride (0.99g; 3.8 mmol) in 10 mL of MeOH was added $NaBH_3CN$ (0.057g; 0.91 mmol) and the mixture was left stirring for 16h at r.t. Another 60 mg of $NaBH_3CN$ was added and left stirring 8 h. The reaction was then poured into $H_2O$-EtOAc (20 mL- 50 mL) and saturated with NaCl. The organic extracts were washed with brine and dry over $Na_2SO_4$. The solvent was removed and the crude product purified by chromatography on silica gel (eluted with 10% → 30% EtOAc in toluene) to yield 0.99g (68%) of the title compound.

$^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3H), 2.46 (m, 4H), 3.59 (s, 2H), 3.67 (m, 4H). 7.02 (t, 1H), 7.20 (m, 3H), 7.40-7.55 (m,2H) and 8.04 (d, 1H).

## EXAMPLE 3

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester

Step 1: 2-Methyl-1H-indol-3-ylacetic acid, methyl ester.

To 2-methyl indole (1.69 g; 12.9 mmol) in 10 mL of THF at 0° C was added MeMgBr 1.4M (12.9 mmol). After 30 min at 0° C. $ZnCl_2$ 1M (12.9 mL; 12.9 mmol) in THF was added and the reaction stirred for an other 30 min at r.t. Methyl bromoacetate (1.4 mL; 14.7 mmol) was added dropwise and left stirring for 48 h. The mixture was poured into aqueous $NaHCO_3$, extracted with EtOAc (3 X 25 mL) and the combined organic extracts were washed with brine. The solution was dried over $Na_2SO_4$ and the solvent removed. Chromatography on silica gel (eluted with 5% EtOAc in hexane) yielded 1.13g (43%) of the title compound.

chloride (0.33 mL; 2.61 mmol) was added and left stirring for 16 hr. It was then poured into cold water-EtOAc (50 mL). The organic phase was washed with $H_2O$ (2 X 15 mL) and brine. The organic phase was dried over $Na_2SO_4$ and the solvent removed. Chromatography on silica gel (eluted with EtOAc) followed by a swish in $CH_2Cl_2$ (hot) - hexane afforded 0.462g (78%) of the title compound.

$^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 3H), 3.44 (m, 4H), 3.61 (s, 4H), 3.66 (s, 2H), 3.80 (s, 3H), 6.67-6.70 (dd, 1H), 6.96 (d, 1H), 7.10 (d, 1H), and 7.39-7.50 (m, 4H).

## EXAMPLE 2

2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole

Step 1: 3-Formyl-2-methyl-1-(1-naphthoyl)-1H-indole

To 3-formyl-2-methylindole (4.30g; 27.0 mmol) in 70 mL of DMF at r.t. was added NaH 80% (0.861 mg). After 30 min of stirring the solution was cooled to 0° C and a solution of 1-naphthoyl chloride (5.04g, 29.3 mmol) in 10 mL of DMF was added dropwise. The mixture was left stirring for 16h at r.t. and poured into cold water-EtOAc (100mL). The organic phase was washed with $H_2O$ (2 X 25 mL) and brine. The organic phase was dried over $Na_2SO_4$ and the solvent removed. Chromatography on silica gel (eluted with 10% EtOAc in toluene) yielded 1.70g (20%) of the title compound.

$^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.64 (s, 3H), 6.95 (d, 1H), 7.04 (t, 1H), 7.10-7.30 (m, 1H), 7.51 (m, 1H), 7.59 (m, 3H), 7.96 (m, 1H), 8.11 (d, 1H) and 10.34 (s, 1H).

(milliliters), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)).

## EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

## EXAMPLE 1

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone

Step 1: 2-[5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]-ethanone

To 5-methoxy-2-methyl-3-indoleacetic acid (0.665g; 3.03 mmol) in 6 mL of THF was added DCC (0.661g; 3.2 mmol). After 2 h of stirring, morpholine (1 mL; 11.4 mmol) was added and stirred for another 1 h. The reaction mixture was filtered and the solvent removed. Chromatography on silica gel (eluted with EtOAc) yielded 0.585g (64%) of the title compound.

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.30 (s, 3H), 3.38 ( m, 4H), 3.60 (m, 4H), 3.70 (s, 2H), 3.82 (s, 3H), 6.7 (m, 1H), 6.93 (s, 1H), 7.09 (d, 1H) and 7.97 (s, 1H).

Step 2: 2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone

To the amide (0.506g ; 1.75 mmol) from step 1 in 10 mL of THF and 0.9 mL of HMPA cooled to -78° C was added KHMDS 0.5 M (3.5 mL; 1.75 mmol) dropwise. The temperature was raised to -22° C for 30 min and brought back to -78° C. Then 2-chlorobenzoyl